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# Relation of Exercise Heart Rate Recovery to Predict Cardiometabolic Syndrome in Men

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Running head: Heart rate recovery predicts metabolic syndrome

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## **Abstract**

We examined the hypothesis that delayed heart rate recovery (HRR) after exercise testing, an estimate of decreased autonomic function, predicts the risk of cardiometabolic syndrome (MetS) and is associated with continuous MetS risk scores in healthy men. Participants were 2,740 men who underwent general health examinations and had no evidence of MetS, cardiovascular diseases, diabetes, and hypertension at baseline. Baseline HRR was calculated as the difference between peak heart rate attained during exercise testing and the heart rate at 1 (HRR 1) and 2 minutes (HRR 2) after test termination. Incident MetS was defined as participants having  $\geq 3$  MetS components, and continuous MetS risk score was computed as the sum of z-score of five risk factors at follow-up. The incidence of MetS was 61/1,000 person-years during an average follow-up of 5 years. The relative risks (RR) and 95% confidence interval (CI) of incident MetS in the lowest quartiles of HRR 1 and HRR 2 vs the highest quartile were 1.24 (95% CI: 1.02-1.51) and 2.02 (95% CI: 1.58-2.60), respectively, after adjusting for potential confounders, including peak oxygen uptake and resting heart rate. HRR 1 ( $\beta=-0.052$ ,  $p=0.005$ ) and HRR 2 ( $\beta=-0.058$ ,  $p=0.009$ ) were independently associated with clustered MetS risk scores after adjusting for covariates. In conclusion, the independent association between delayed HRR after exercise testing and incident MetS and continuous MetS risk scores suggests that decreased autonomic function may be considered as a parameter to predict the future likelihood of MetS.

*Key words: Heart rate recovery, autonomic function, and metabolic syndrome*

## **Introduction**

Delayed heart rate recovery (HRR) after maximal exercise testing, an estimate of decreased autonomic nervous system activity, is a prognostic indicator that is strongly associated with adverse cardiometabolic outcomes.<sup>1-4</sup> Moreover, this finding is associated with central obesity<sup>5,6</sup> and insulin resistance,<sup>7</sup> both of which are major contributors to incident cardiometabolic syndrome (MetS). Although cross-sectional studies have demonstrated that delayed HRR after exercise testing is associated with the presence of MetS,<sup>5,8,9</sup> it remains unclear whether this association persists in longitudinal investigations of healthy populations. Further, it remains unclear whether delayed HRR is prospectively associated with continuous clustered MetS risk scores using standardized residuals (z score), which comprise the dichotomous definition of MetS.<sup>10,11</sup> We investigated whether delayed HRR after peak or symptom-limited cardiopulmonary exercise testing would predict incident MetS, independent of confounders, in initially healthy men without MetS. Additionally, we examined the hypothesis that HRR is prospectively associated with the continuous clustered MetS risk scores at follow-up.

## **Methods**

From a large cohort of participants who underwent general health examinations in 1998 at Samsung Medical Center (Seoul, Republic of Korea), we evaluated 2,740 men (mean age 48 years; range 20–76) who had no evidence of MetS, cardiovascular diseases, diabetes, and hypertension at baseline, all of whom had undergone peak or symptom-limited cardiopulmonary exercise testing. Participants were followed for an average of 5 years after their baseline examination. Written informed consent was obtained from all participants before the health screening program, and the study was approved by the

medical center institutional review board. Body mass index (BMI) was calculated as weight (kg) divided by height squared ( $m^2$ ). Resting blood pressure (BP) was obtained in the seated position following  $\geq 5$  min of quiet rest using an automated sphygmomanometer (Dinamap PRO 100, Milwaukee, WI, USA). The lowest value of two measurements was used as resting BP. Blood samples were collected in the morning following a 12-h overnight fast and analyzed by the hospital clinical laboratory. Detailed methods of blood analysis have been previously described.<sup>12</sup>

MetS was defined as participants having  $\geq 3$  of the following risk factors: waist girth  $>90$  cm, systolic/diastolic blood pressure (SBP/DBP)  $>130/85$  mmHg, high-density lipoprotein cholesterol (HDL-C)  $<40$  mg/dL, triglycerides  $>150$  mg/dL, or glucose  $>100$  mg/dL at baseline and follow-up examinations based on the National Cholesterol Education Program's adult treatment panel III criteria and WHO Asia-Pacific obesity criteria for waist circumference. To achieve greater statistical power,<sup>10</sup> we additionally computed continuous clustered cardiometabolic syndrome risk scores using standardized residuals (z score) for the following variables: waist girth, mean arterial pressure ((SBP-DBP)/3+DBP), HDL-C (the calculation was multiplied by -1 since a low value is unfavorable), triglycerides, and glucose.<sup>11,13</sup> We calculated the sum of the z-scores from these variables, with a lower score indicating a more favorable MetS profile.

Resting HR was measured in the supine position using an electrocardiogram (Hewlett-Packard ECG M 1700A, WI) following at least 5 min of quiet rest. Participants performed peak or symptom-limited treadmill exercise testing using the conventional Bruce protocol. Cardiorespiratory fitness was directly measured using a calibrated, automated metabolic measurement system (Jaeger Oxycon Delta, Erich Jaeger,

Höechberg, Germany) using a breath-by-breath method to determine the highest attained oxygen uptake value during progressive testing to volitional fatigue. Exercise tests were terminated for any of the following reasons: a rating of perceived exertion >17 (very hard work); achievement of >90% of age-predicted maximal HR; participant request, secondary to volitional fatigue; and, SBP >250 mm/Hg. Peak HR was determined from 12-lead electrocardiograms (Quinton Q-4500, Bothell, WA) and defined as the highest value achieved during the exercise test. The recovery protocol consisted of 2-min of slow walking with no incline (1.2 mph, 0% grade) immediately after peak exercise testing. HRR was calculated as the difference between peak HR during exercise testing and the heart rate at 1 (HRR 1) and 2 minutes (HRR 2) after test termination.

Descriptive statistics were expressed as mean and standard deviation or percentage. Either student *t*-tests or chi-squared comparisons were used for all variables to evaluate the within and between group changes among those with and without incident MetS at follow-up. Pearson correlations and multiple linear regression analysis were used to evaluate the independent associations of HRR 1 and HRR 2 at baseline with continuous MetS risk scores at follow up. To test for the associations between exercise HRR and the development of MetS, participants were divided into quartiles according to the decrement in HR immediately after exercise testing. Mean comparisons of continuous MetS risk score by HRR quartiles were performed using ANOVA. Cox proportional hazards regression with adjustment for confounders was used to determine the effect of HRR as a categorical and/or continuous variable (per 1 bpm difference) on the incidence of MetS and for each of the MetS components.

We also examined a potential non-linear dose-response relationship between HRR and MetS using restricted cubic spline functions with 4 knots at the 5th, 35th, 65th and 95th percentiles of the HRR distribution in a multivariate adjusted model.<sup>14</sup> Statistical significance was set at  $p < 0.05$ . All tests for statistical significance were two-sided. Statistical analyses were conducted using the SPSS 21.0 (SPSS, Armonk, NY: IBM Corp).

## **Results**

Baseline demographic characteristics and cardiometabolic risk factors of participants with and without MetS at follow-up are presented in Table 1. BMI, resting HR, total cholesterol, low-density lipoprotein cholesterol, uric acid, white blood cell counts, and all components of MetS were higher, whereas HDL-C, and peak oxygen uptake were lower in participants who developed MetS. Participants with MetS were also more likely to demonstrate lower HRR 1 and HRR 2 than participants without MetS ( $p < 0.05$ ).

During an average follow-up of 5 years, 845 (30.8%) participants developed MetS, and the incidence of MetS was 61/1,000 person-years. Table 2 shows that the relative risk (RR) and 95% confidence interval (CI) of incident MetS by HRR 1 as a categorical and/or continuous variable. The RR of incident MetS in the lowest HRR 1 quartile (Quartile 1) vs the highest HRR 1 quartile (Quartile 4) was 1.24 (95% CI: 1.02-1.51) after adjusting for age, white blood cell counts, uric acid, smoking, alcohol intake, BMI, peak oxygen uptake and resting heart rate. Each increment in HRR 1 (1 bpm decrease) was not statistically associated with a lower incidence of MetS after adjusting for covariates (RR: 0.99; 95% CI: 0.98-1.00,  $p = 0.06$ ). The RR of incident MetS in the lowest quartile of

HRR 2 vs the highest quartile of HRR 2 was 2.02 (95% CI: 1.58-2.60) after adjusting for the above-referenced confounders. Each increment in HRR 2 (1 bpm decrease) was associated with a 2% lower risk of incident MetS after adjusting for covariates (Table 3). In addition, the association between the incidence of each MetS component and HRR quartiles revealed that all variables, except waist girth, were significant across HRR quartiles after adjusting for covariates (supplementary Table 1).

In Figure 1A, the restricted cubic spline curve suggests a linear inverse association between HRR 1 and MetS (\*p\*for non-linearity=0.344). Figure 1B suggests a non-linear relationship between HRR 2 and MetS (\*p\*for non-linearity=0.006).

In an analysis of HRR quartiles to the continuous clustered metabolic risk scores, mean values of the sum of continuous metabolic risk scores showed significant differences across HRR 1 quartile (p=0.001) and HRR 2 quartile (p=0.002) (Supplementary table 2). The sum of continuous metabolic risk scores was negatively correlated with HRR 1 (r = -0.063, p<0.01) and HRR 2 (r = -0.057, p<0.05) (Supplementary table 3). Table 4 shows that both HRR 1 (standardized  $\beta$  = -0.052, 95% CI -0.029, -0.005, p=0.005) and HRR 2 (standardized  $\beta$  = -0.058, 95% CI -0.023, -0.003, p=0.009) were prospectively associated with the standardized components of a continuous metabolic risk score (table 4).

## **Discussion**

The present findings demonstrate that delayed HRR after exercise testing was associated with incident MetS after adjusting for potential confounders, including peak oxygen uptake and resting heart rate, both of which are important confounding variables to HRR.<sup>2</sup> The present study results also showed that the risk of MetS seems to decrease



gradually in a linear dose-response manner with increasing HRR 1 beyond a value of 21 bpm. However, there was no increase or decrease in the risk of MetS at HRR 2 values between 12 bpm and 42 bpm, with a subsequent decrease in MetS risk with increasing HRR 2 beyond a value of 42 bpm.

We added an analysis of HRR with a continuous clustered MetS risk score and found that both HRR 1 and HRR 2 were independently associated with it after adjusting for covariates. These results are consistent with two cross-sectional studies which reported that HRR was inversely associated with metabolic risk scores in healthy children and adolescents.<sup>15,16</sup> Therefore, our findings extend these results to healthy adults using a prospective study design.

Interestingly, we found that the risk of incident MetS was nearly doubled in HRR 2 versus HRR 1. Our results are consistent with a previously published meta-analysis noting that HRR 2 is more closely related to the risk of cardiovascular events and all-cause mortality than HRR 1.<sup>17</sup> In contrast, other meta-analysis have reported that HRR 1 might be more sensitive in predicting incident type 2 diabetes than HRR 2.<sup>18</sup> Such inconsistencies make it difficult to confirm or refute our results and suggest that these differences may be attributed, at least in part, to the population under investigation, differing risk factor profiles at baseline, variations in study methodology, or combinations thereof. Clearly, additional studies are needed to clarify why HRR 2 may be more sensitive in predicting the risk of MetS.

In contrast to our results, Kizilbash et al.<sup>19</sup> reported that despite the cross-sectional association between delayed 2 minute exercise HRR and incident MetS, this finding did not precede the development of MetS, but appeared only after participants (aged 18-30

years) exhibited syndrome components in the Coronary Artery Risk Development in Young Adults study. These conflicting data may be due to differing definitions for MetS, age differences in our respective study populations, or both. In their study, the presence of MetS was defined using  $\geq 2$  components. Accordingly, the need to further clarify the longitudinal association between delayed HRR and incident MetS using the definition of  $\geq 3$  components is apparent.

Although the mechanisms underlying the association between delayed HRR and incident MetS in the present study are not fully understood, there are several possible explanations. Delayed HRR after peak or symptom-limited exercise testing may reflect impaired parasympathetic reactivation.<sup>1,2,20</sup> Decreased autonomic function has been associated with an increased risk of incident hypertension<sup>21,22</sup> and type 2 diabetes,<sup>18</sup> both of which are linked to an increased risk of MetS. In addition, several studies have now reported that decreased autonomic function and/or delayed HRR are associated with elevations in cardiometabolic risk factors, including central obesity,<sup>5,6</sup> insulin resistance,<sup>7</sup> dyslipidemia,<sup>23</sup> and inflammation,<sup>24</sup> all of which are considered pathogenic components of the MetS. In addition, reduced parasympathetic activity increases number of adverse metabolic components and may provide a plausible explanation for the linkage between delayed HRR and MetS incidence.<sup>25</sup> Further studies are needed to better clarify the underlying biologic mechanisms responsible for the delayed HRR in MetS.

We acknowledge several methodological limitations to our study. Our study population included only men, which limits the generalizability of our findings to women. Additional studies are needed to clarify the potential impact of sex in the association between delayed HRR and incident MetS. We did not control for dietary habits, which

may potentially confound the association between delayed HRR and incident MetS. Although our participants were apparently healthy, we didn't control for left ventricular systolic/diastolic dysfunction and chronic obstructive pulmonary disease, both of which may potentially confound the association between delayed HRR and incident MetS.<sup>26,27</sup> Although we adjusted for potential confounders to establish an independent association between HRR and MetS, it is possible that residual variables that were not measured or accounted for may have influenced the observed differences in RRs. Finally, we used a single assessment of HRR, did not assess the reproducibility of HRR in our study population, and acknowledge that data for the 2-minute HRR quartiles were incomplete (n = 1,989). Despite these limitations, strengths of this prospective study were that we adjusted for directly measured peak oxygen uptake, which is an important confounding variable regarding the association between delayed HRR and incident MetS.

### **Disclosures**

The authors report no relations that could be construed as a conflict of interest.

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### **Figure legend**

Figure 1. The dose-response relationship between heart rate recovery and MetS using restricted cubic spline functions with 4 knots at the 5th, 35th, 65th and 95th percentiles of the heart rate recovery distribution in a multivariate adjusted model. Adjusted relative risks by solid lines and 95% confidence intervals by dashed lines are reported. A: heart rate recovery at 1 minute. B: heart rate recovery at 2 minutes.